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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,996	12/30/1999	JOHANNES CHRISTIANUS VAN GROENINGHEN	49477(1958)	3246

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EXAMINER	
BORGEEST, CHRISTINA M	
ART UNIT	**PAPER NUMBER**
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/446,996	VAN GROENINGHEN, JOHANNES CHRISTIANUS	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12 and 14-20* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment filed 23 May 2007 is acknowledged. Claims 14 and 19 are amended. Claims 1-9 and 12 are withdrawn. Claims 10-11 and 13 are cancelled. Claims 14-20 are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 103

The rejection of claims 14, 16, 18, 19 and 20 rejected under 35 U.S.C. 103(a) as being unpatentable over He et al. (1986, Clinical Chemistry, Vol. 32, No. 6, pp. 1159, abstract #542—cited in Applicant's 1449 form from 17 August 2005) is withdrawn in response Applicant's argument (at p. 11, 1st paragraph of the response filed 23 May 2007) that H3-thymidine and uridine incorporation was increased. Given that it is known in the art that H3-thymidine incorporation is used to determine DNA synthesis, the results by He et al. are contradictory, since they also teach a decrease in cell growth. Given this contradiction, the person of ordinary skill in the art (POSITA) would not find motivation to treat melanoma with a GnRH antagonist, nor would it be predictable that applying a GnRH antagonist to treat GnRH positive tumors would have a reasonable expectation of success based on the findings of He et al.

Rejections Maintained

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 14-20 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing cellular replication of a GnRH-receptor positive malignant melanoma comprising administering a GnRH agonist, or optionally, a GnRH agonist in combination with a cytotoxic substance, does not reasonably provide enablement for the methods as broadly claimed is ***withdrawn in part and maintained in part***. Claims 14-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for decreasing cellular replication of GnRH-receptor positive oat cell carcinoma, GnRH-receptor positive malignant melanoma or GnRH-receptor positive Kaposi sarcoma, said method comprising administering to said subject a replication decreasing amount of one or more of a GnRH agonist or GnRH antagonist, said GnRH agonist or antagonist being a GnRH analogue, wherein said analogue is leuprorelin, triptorelin, buserelin goserelin, cetrorelix (or one of the analogues listed in Table I), or optionally, a method for decreasing cellular replication of GnRH-receptor positive oat cell carcinoma, GnRH-receptor positive malignant melanoma or GnRH-receptor positive Kaposi sarcoma, said method comprising administering to said subject a replication decreasing amount of one or more of a GnRH agonist or GnRH antagonist, said GnRH agonist or antagonist being a GnRH

analogue in combination with a cytotoxic substance, wherein said analogue is leuprorelin, triptorelin, buserelin goserelin, cetrorelix (or one of the analogues listed in Table I), does not reasonably provide enablement for the claims as broadly recited.

Applicant's arguments in the response filed 23 May 2007 at p. 7, 3rd paragraph that Moretti et al. had to use a lower dose of antagonist, because administration of higher doses of the GnRH antagonist, ANTIDE™, was inhibitory is persuasive (i.e., Moretti used subclinical doses of ANTIDE™ to block activity of the agonist, but the dose had to be low enough so that ANTIDE™ itself would not block tumor growth). Furthermore, the declaration submitted under 37 CFR 1.132 filed 23 May 2007 does provide guidance as to where in the specification of copending Application No. 10/327,621 there is support that oat cell carcinoma and Karposi sarcoma are GnRH positive (i.e., the scope of what is enabled is broader than only GnRH positive melanoma). In addition, Applicant has provided evidence in the previous response (filed 4 August 2006) in the form of articles by Pinski et al. and Vincze et al. that support the use of GnRH antagonists for the treatment of gynecological cancers. Thus, it is persuasive that ***certain*** GnRH agonists and ***certain*** antagonists are indicated for use in GnRH positive tumors. Applicant's arguments and evidence were partially persuasive, and thus the instant scope rejection indicates that a larger scope of the instant claims is considered to be enabled, however, Applicant's arguments and evidence provided in the response were not persuasive to withdraw the entire rejection, as discussed below.

Applicant's arguments presented in their response filed 23 May 2007 do not address the concerns regarding the breadth of GnRH analogues, but rather are

concerned with arguing that both GnRH agonists and antagonists are used in cancer therapy (see p. 6, 3rd paragraph of the Remarks, for example). Since this issue has been resolved, the arguments are not applicable to the current rejection. However, not all analogues are considered to be enabled. The claims recite "GnRH analogue", which is very broad and encompasses agents not yet discovered. The claims are drawn to treatment of GnRH positive tumors in a subject (i.e., in vivo), and the efficacy of any particular compound is dependent upon many variables, including pharmacological and physiological, as well as biochemical factors. Because of the complex nature of all of these factors, it is not predictable which analogues would function as claimed. Unlike a screening method, the claims are drawn to treatment, which is complex and involves an undue amount of experimentation to make (in the instant case, to discover) and test every possible analogue encompassed by the claims. Furthermore, the enablement requirement of 35 U.S.C. 112, first paragraph stipulates one of ordinary skill in the art to make and use the invention, rather than make and test. The specification discloses only those agents listed in Table I (leuprorelin, triptorelin, buserelin goserelin, cetrorelix, ANTARELIX™, ANTIDE™, RAMORELIX™), however, these representative examples of GnRH analogues listed are not commensurate in scope with claiming that an entire genus could be used to treat cancer Finally, the declaration submitted under 37 CFR 1.132 filed 23 May 2007 is insufficient to overcome the rejection of claims 14-20 under 35 U.S.C. 112, first paragraph, as set forth in the previous Office actions because Applicant does not address the Examiner's concerns with regard to the breadth of what is claimed (i.e. treatment comprising administration of any GnRH analogue).

Due to the large quantity of experimentation necessary to make the vast number of encompassed GnRH analogues and test the same for the ability to treat GnRH positive tumors in a subject, the lack of direction/guidance presented in the specification and the absence of working examples regarding how to make all the encompassed GnRH analogues, the complex nature of the invention (treatment of cancer), and the breadth of the claims which fail to recite structural limitations on GnRH analogues, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 14 and 19 under 35 U.S.C. 102(b) as being anticipated by Laue et al. (AJDC. 1985; 139: 1097-1100—cited in Applicant's 1449 form from 17 August 2005) is maintained for reasons of record and the following.

Applicant argues at p. 8, last paragraph that the standards under which the PTO is permitted to advance an "inherency" rejection are ***extremely*** high," and cite numerous examples of case law (see pages 8-10).

Applicant argues at p. 10, 2nd paragraph that Laue teaches nothing about the condition of optic gliomas, nor the effect of LHRH analog therapy on these lesions, thus

in order for the Examiner to advance the rejection, it must be that the treatment necessarily resulted in an impact on the optic gliomas. Specifically, Applicant argues it is unknown whether gliomas were (a) already drug resistant, (b) generally insulated from treatments given in the route(s) as reported, or (c) insufficiently vascularized to receive LHRH analogs regardless of route and finally that the subcutaneous route was used.

These arguments have been fully considered but are not found persuasive. Regarding In re Rijckaert, 28 USPQ2d 1955 (Fed. Cir. 1993), this case had to do with a rejection made under 35 U.S.C. 103, and thus the fact pattern is not the same as in the instant case, in which the claims were rejected under 35 U.S.C. 102(b). Regarding In Re Robertson, 49 USPQ2d 1949 (Fed. Cir. 1999) and Ex Parte Levy, 17 USPQ2d 1461 (Bd. Pat. App. & Int. 1990), Laue et al. teach the administration of an LHRH agonist analog (LHRHa: D-Trp^{6}-Pro^{9}-NEt-LHRH) to patients suffering from optic glioma (see p. 1097, under Patients and Methods and Protocol), thus Laue and colleagues teach administration of the same compound to the same patient population, therefore, any effect of LHRH antagonist purported would necessarily have the same effect regardless of whether all of the effects were appreciated at the time of the reference. It is not necessary for a reference to appreciate all of the mechanisms of action in order to anticipate. Note that the rejection is not an obviousness type rejection, but rather an anticipation rejection. See MPEP 2112 [R-3]:

> II. INHERENT FEATURE NEED NOT BE RECOGNIZED AT THE TIME OF THE INVENTION
>
> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but

> only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); Abbott Labs v. Geneva Pharms., Inc., 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999) ("If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics."); Atlas Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) ("Because sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known.")>; SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)

Thus, Applicant's arguments that it was unknown whether gliomas were (a) already drug resistant, (b) generally insulated from treatments given in the route(s) as reported, or (c) insufficiently vascularized to receive LHRH analogs regardless of route are not relevant. The issue is that the same patient population was treated with the same compound, thus the claims are anticipated.

Also, note *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226 (CCPA1971) indicating that a more relaxed burden may apply to the examiner's establishing a *prima facie* case of inherency in making a prior art rejection. In order for the examiner to assert inherency there must merely be a reasonable basis to believe that the feature is

present in the prior art, thus shifting the burden to applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied upon. See also *In re Best*, 562 F.2d 1252, 195 USPQ 430, 443 (CCPA 1977); *In re Schreiber*, 128 F.3d 1473, 1478, 44 USPQ2d 1429 (Fed. Cir. 1997).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 14-20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-40, 50 and 51 of copending Application No. 10/327,621 is maintained for reasons of record as set forth at pages 12-13 in the Office action mailed 26 February 2007. It is noted that Applicant has not responded to this rejection, however, deferral of arguments is not proper; an

argument after the claims have been found otherwise allowable that obviousness type double patenting does not exist will not be considered timely. Accordingly, the provisional rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646